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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,536	02/26/2004	Arthur M. Krieg	C1039.70083US05	9640

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,536	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 37-56 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 37-56 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 7 sheets

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/26/05. 7 sheets

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of species X_1= A, X_2 = A, X_3 = T, and X_4 = T (AACGTT) in the reply filed on November 4, 2004 is acknowledged.
Claims

2. The disclosure is objected to because of the following informalities: some of the sequences in the specification do not have a sequence identifier, for example see p. 4, l. 35 and p. 13, l. 21; p. 11, l. 6-7 a parenthesis is missing; incomplete sentence on p. 10, l. 30-31. Applicants should review the entire specification and correct any errors so that there will not be a delay in issuing the allowed application (assuming allowable subject matter has been identified). Appropriate correction is required.

3. The information disclosure statement filed February 26, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Please note, cited prior applications (09/415142 and 10/690495) have been reviewed for cited references on the February 26, 2004 IDS. Prior application, 08/386063, is not available to the Examiner. The Examiner has considered and initialed the references that could be obtained. A copy of those references not

initialed should be provided for consideration is Applicants want all references on the IDS to be cited on an issued patent.

4. Claims 37-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering CpG to a subject (mice), does not reasonably provide enablement for a method for stimulating a subject's response to a vaccine comprising administering an immunostimulatory oligonucleotide adjuvant as a vaccine adjuvant to the subject to stimulate the subject's response to the vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The presently pending claims are not clear with regard to the intended use as well as the steps comprising the claimed method. For example, it is not clear if the composition being administered to the subject comprises the immuno-stimulatory oligonucleotide or the immunostimulatory oligonucleotide and a vaccine antigen? Is the CpG administered before the vaccine antigen? What does Applicant intend for the recitation of "response to a vaccine"? It is not clear if response means stimulating an immune response or stimulating a vaccine to protect the subject against infection. A review of the specification does not answer these questions and in view of these questions, the specification is not enabled for the scope of the claimed invention.

Example 5 of the specification teaches in vivo studies with CpG phosphorothioate ODN. "Mice were weighed and injected IP with 0.25ml of sterile PBS or the indicated phosphorothioate ODN dissolved in PBS. Twenty four hours later, spleen cells were harvested, washed, and stained for flow cytometry

using phycoerythrin conjugated 6B2 to gate on B cells in conjunction with biotin conjugated anti Ly-6A/E or anti-Iad (Pharmingen San Diego, CA) or anti-Bla-1 (Hardy, R. R. et a1., J. Exp. Med. 159:1169 (1984). Two mice were studied for each condition and analyzed individually." (specification, p. 27)

It is not clear if this study was actually done. The methods and steps have been set forth, but data indicating the results of this study are disclosed in this specification. There does not appear to be any example set forth of administering a vaccine composition (i.e. antigen and CpG) to a subject and the resultant stimulating a subject's response to a vaccine.

The scope of the recitation "vaccine" is broad and the claims do not specifically define a particular vaccine or antigen for the vaccine. Does applicant intend this method to be applied to each and every vaccine composition (i.e. viral, bacterial, fungal, protozoal, cancer, etc)? The specification at p. 7 indicates that the immunostimulatory oligonucleotides can be used to treat, prevent or ameliorate an immune system deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject; and that the CpG can be administered as a vaccine adjuvant to stimulate a response to a vaccine. As previously stated, the specification does not set forth enablement for the scope of the claimed invention, or for the statements in the specification regarding treatment, prevention or amelioration..

The state of the art regarding the use and function of immunostimulatory oligonucleotides is unpredictable. At the time the pending patent application was filed, 1995, the state of the art was unpredictable regarding the immuno-stimulatory oligonucelotides (CpG) and its use as an adjuvant, immunopotentiator, or as a compound alone to treat, prevent or ameliorate an immune system

deficiency (e.g. tumor or cancer or a viral, fungal, bacterial or parasitic infection) in a subject. Threadgill et al 1998 teaches that oligonucleotides containing stimulatory unmethylated CpG dinucleotides may not be useful adjuvants when given simultaneously with bacterial PS vaccines (abstract). The oligonucleotide would not be useful in a method of stimulating a response in a subject to a bacterial vaccine. Polysaccharide-specific antibody levels were reduced in mice coadministered CpG and high-MW PS as compared to mice administered high-MW PS with NSCpG oligo or PS alone without an adjuvant (p. 80). Threadgill et al states that based on in vitro and short term in vivo experiments, some investigators have suggested that oligonucleotides containing CpG motifs could be used as adjuvants for inducing an improved immune response to normally poor immunogens (p. 77). However, Threadgill et al, in 1998, states that more experimentation in animals should provide the information necessary to evaluate more fully the potential of CpG oligos as a vaccine adjuvant (p. 81).

The state of the art after the filing date of the claimed invention appears to indicate that CpG functions as an adjuvant in some viral compositions (see for example Gallichan et al, 2001 and Harandi et al, 2004). However, the state of the art at the time of the invention did not indicate or suggest the use of a vaccine composition comprising CpG or CpG alone in the scope of the methods presently claimed. Further, there are numerous possible immunostimulatory oligonucleotide sequences within the scope of the claimed CpG and it is not clear that each one would function as claimed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation

necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Regarding points 1-3, the pending specification does not provide sufficient evidence of a working example and as a result this would require undue experimentation for the person of skill in the art to practice the claimed invention. The state of the art, the unpredictability of the art and the scope of the invention have been discussed above. In view of all of the above, it would require undue experimentation for the skilled artisan to practice the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 37 and 46-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Tokunga et al (EP 468520 A2).

Tokunga et al discloses an immunostimulatory oligonucleotide of 10-100 bases having a specific formula that shows strong immunostimulatory activity (abstract). The prior art discloses immunostimulatory remedies capable of arresting and curing susceptible to medicines having immunopharmacological activity (p. 2). Tokunga et al discloses oligonucleotides comprising the AACGTT sequence (elected species) (see p. 3). Tokunga et al discloses that the immunostimulatory remedies can be used alone or in combination with other therapeutic means against such diseases the outbreak of which can be suppressed,

or the progress of which can be arrested or delayed, by the functions of the immune system and lists numerous diseases and conditions (p. 4). The examples disclose method of administering the CpG to a subject and administering the CpG and an antigen to a subject (see examples).

The prior art discloses the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicants' methods with the methods of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed methods and the methods of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. It is noted that Applicants have numerous patent applications claiming various compositions and methods using the immunostimulatory oligonucleotides of the presently claimed invention. The Examiner requests that Applicants identify those pending applications that are related to the claimed invention and having pending related claims in order to avoid ODP situations.

8. No claims are allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is

571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
February 7, 2005